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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/744,432	01/22/2001	Jeffrey Clayton Baker	X-11634	5090

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EXAMINER	
MOHAMED, ABDEL A	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 02/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/744,432	BAKER ET AL.	
	Examiner	Art Unit	
	Abdel A. Mohamed	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 December 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

ACKNOWLEDGMENT OF REMARKS, IDS AND STATUS OF THE CLAIMS

1. The remarks and information disclosure statement (IDS) and Form PTO-1449 filed 12/3/03 are acknowledged, entered and considered. Claims 1-8 are now pending in the application. The rejections under 35 U.S.C. 102(b) and under 35 U.S.C. 103(a) over the prior art of record are maintained.

CLAIMS REJECTION-35 U.S.C. § 102(b)

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) The invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 5 and 6 remain rejected under 35 U.S.C. 102(b) as being anticipated by Foster et al. (U.S. Patent No. 5,516,650).

The reference of Foster et al. discloses lyophilization (freeze-drying) of activated protein C, wherein the activated protein C is a human activated protein C (e.g., abstract and col. 9, lines 62 to col. 10, lines 5). Thus, in the absence of evidence to the contrary or specific structural limitations, the claimed formulation/product disclosed by the reference anticipates claims 5 and 6 as drafted.

CLAIMS REJECTION-35 U.S.C. § 103(a)

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-8 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Tse et al. (U.S. Patent No. 5,716,645) taken with Foster et al. (U.S. Patent No. 5,516,650).

Tse et al. teach similarly as the instantly claimed invention the use of a cryoprecipitate or cryogranulate procedure to prepare a stable fibrinogen composition from human origin, which contains a high concentration of fibrinogen and very low levels of Factor VIII (FVIII). The dissolved cryoprecipitate is cooled to about 10 degrees C to

form cold precipitate, and then, the cold precipitate is freezed into cryogranulates at –60 degrees C or lower (i.e., frozen in liquid nitrogen) as directed to claims 1-6 (See e.g., cols. 1, lines 55 to cols. 4, lines 11 and Example I).

Although, the reference of Tse et al. does not specifically mention activated protein C, however, the reference clearly teaches the preparation of dissolved cryoprecipitate activated fibrinogen and FVIII. The activated fibrinogen and FVIII include the specific activated protein C since they are generic. For further support See e.g., the instant specification on page 1, lines 9-17 which acknowledges that protein C is a serine protease and naturally occurring anticoagulant that plays a role in the regulation of homeostasis by inactivating Factors Va and VIIIa in the coagulation cascade. Human protein C circulates as a 2-chain zymogene which is inactivated *in* vivo by thrombin and thrombomodulin on phospholipid surface resulting in activated protein C. Thus, in view of the above, the fibrinogen complex taught by the prior art of Tse et al. clearly encompasses the instantly claimed activated protein C.

Tse et al. differ from claims 1-8 in not teaching a process of preparing a lyophilized formulation of activated protein C and the addition of a pharmaceutical acceptable bulking agent. With respect to lyophilization process, the reference of Tse et al. clearly teaches the use of lyophilized fibrinogen complex (See e.g., Figure I and col. 10, lines 1-4); however, the general method of lyophilization of protein pharmaceutical and the addition of a pharmaceutical bulking agent is conventional and within the ordinary skill in the art to which this invention pertains to lyophilize and add a pharmaceutically acceptable bulking agent of any protein of interest. Nevertheless, the

lyophilization and the addition of a pharmaceutically acceptable bulking agent of activated protein C is clearly disclosed by the secondary reference of Foster et al. on col. 4, lines 1-5 and col. 9, lines 62 to col. 10, lines 5, as directed to claims 5-8. Thus, those skill in the art will know the employment of other bulking agent (such as sucrose) for activated protein C for use in the formulations of the invention and their effective concentrations.

Therefore, in view of the above, one of ordinary skill in the art would have been motivated to adapt the well known lyophilization process and addition of pharmaceutically acceptable bulking agent scheme of Foster et al. secondary reference into the method of Tse et al. primary reference because including such features into the method of Tse et al. reference would have been obvious to one of ordinary skill in the art to obtain the known and recognized functions and advantages of addition of bulking agents thereof. Thus, the combined teachings of the prior art makes obvious a process of preparing cryogranules of activated protein C and a lyophilized formulation having a pharmaceutically acceptable bulking agent thereof, absence of sufficient objective factual evidence or unexpected results to the contrary.

ARGUMENTS ARE NOT PERSUASIVE

4. The rejection of claims 5 and 6 under 35 U.S.C. 102(b) as being anticipated by Foster et al. (U.S. Patent No. 5,516,650).

Applicant's arguments filed 9/26/03 have been fully considered but they are not persuasive. Applicant has argued that Foster does not contain cryogranules of activated protein C and Foster does not disclose all elements of the claims and, hence, does not anticipate the claimed invention is unpersuasive. Contrary to Applicant's arguments, claims 5 and 6 are directed to cryogranules of activated protein C, wherein the activated protein C is human activated protein C. As admittedly acknowledged on page 2 of Applicant's response filed 12/3/03 that Foster contains reference to lyophilizing the protein C or activated protein C of Foster's invention. Lyophilization, also known as freeze-drying which is a process of isolating a solid substance (e.g., granules, pellets, particles, etc.) from solution by freezing (e.g., cryo) the solution and sublimating the ice under vacuum. Similarly, cryo is defined in the dictionary as cold, freezing and on page 3, lines 31-33 in the instant specification Applicant defines cryogranules as frozen, discrete granules from solution or slurries of solid substance (e.g., activated protein C) formed after contact with a cryogenic (cryogenic is defined in the dictionary as relating to low temperatures) material such as liquid nitrogen. Thus, in view of Applicant's acknowledgments and in view of the relations of freeze-drying, lyophilization and cryogranulation as defined by Medical Dictionary, one of ordinary skill in the art would understand that these three techniques are not distinct from each other as argued by Applicant because each process is directed to a method of tissue preparation in which the tissue specimen is frozen and then dehydrated at low temperature in a high vacuum or to the creation of a stable preparation of biological substances (blood, plasma, serum, etc.) by rapid freezing and dehydration of the frozen

product under high vacuum (See e.g. page 897 of Donald's Medical Dictionary). Therefore, the reference of Foster et al. discloses the lyophilized preparation (freeze-dried or cryogranulated) of activated protein C, wherein the activated protein C is a human activated protein C as disclosed on col. 9, lines 62 to col. 10, lines 5. Thus, in the absence of evidence to the contrary or specific structural limitations, the claimed formulation/product disclosed by the reference anticipates claims 5 and 6 as drafted.

5. The rejection of claims 1-8 under 35 U.S.C. 103(a) as being unpatentable over Tse et al. (U.S. Patent No. 5,716,645) taken with Foster et al. (U.S. Patent No. 5,516,650).

Applicant has argued that none of the cited references either singularly or in combination disclose all the claims limitations. In particular, the Examiner's attention is drawn to the fact that Applicant has used cryogranulation to remedy these activated protein C (aPC) manufacturing issues. Tse, on the other hand, teaches the use of plasma that is cryogranulated and then used to prepare fibrinogen composition essentially free of FVIII. Furthermore, the Examiner notes that Tse does not mention aPC. However, the Examiner then states that "[t]he activated fibrinogen and FVIII include the specific activated protein C since they are generic. Further, Applicant asserts that the terms "activated fibrinogen" and "FVIII" refer to two proteins that are completely unlike protein C and aPC because the homology between human protein C and fibrinogen as well as between human protein C and FVIII is low. As such, these terms are not generic terms encompassing protein C or aPC is unpersuasive.

Contrary to Applicant's arguments, the Examiner has clearly indicated as discussed above that the primary reference of Tse et al. teaches similarly as the instantly claimed invention the use of a cryoprecipitate or cryogranulate procedure to prepare a stable fibrinogen composition from human origin, which contains a high concentration of fibrinogen and very low levels of Factor VIII (FVIII). The dissolved cryoprecipitate is cooled to about 10 degrees C to form cold precipitate, then, the cold precipitate is freezed into cryogranulates at –60 degrees C or lower (i.e., frozen in liquid nitrogen) as directed to claims 1-6 (See e.g., cols. 1, lines 55 to cols. 4, lines 11 and Example I).

Although, the reference of Tse et al. does not specifically mention activated protein C, however, the reference clearly teaches the preparation of dissolved cryoprecipitate activated fibrinogen and FVIII from plasma. The activated fibrinogen and FVIII include the specific activated protein C since they are generic. For further support See e.g., the instant specification on page 1, lines 9-17 which acknowledges that protein C is a serine protease and naturally occurring anticoagulant that plays a role in the regulation of homeostasis by inactivating Factors Va and VIIIa in the coagulation cascade. Human protein C circulates as a 2-chain zymogene which is inactivated *in* vivo by thrombin and thrombomodulin on phospholipid surface resulting in activated protein C. Thus, in view of the above, the fibrinogen complex taught by the prior art of Tse et al. clearly encompasses the instantly claimed activated protein C because all are derived from blood plasma regardless of their intended use.

Further, the reference of Tse et al. does not teach a process of preparing a lyophilized formulation of activated protein C and the addition of a pharmaceutical acceptable bulking agent. However, with respect to lyophilization process, the reference of Tse et al. clearly teaches the use of lyophilized fibrinogen complex (See e.g., Figure I and col. 10, lines 1-4); furthermore, the general method of lyophilization of protein pharmaceutical and the addition of a pharmaceutical bulking agent is conventional and within the ordinary skill in the art to which this invention pertains to lyophilize and add a pharmaceutically acceptable bulking agent of any protein of interest. With respect to Applicant's arguments that neither reference teaches the cryogranulation of aPC or thawing aPC cryogranules to from a solution before using a bulking agent and lyophilization. These arguments are irrelevant because step (b) of claim 7 is directed to "***optionally*** adding a pharmaceutically acceptable bulking agent to said solution". Hence, Applicant's arguments are directed to a step which is optional. Nevertheless, the lyophilization and the addition of a pharmaceutically acceptable bulking agent of activated protein C is clearly disclosed by the secondary reference of Foster et al. on col. 4, lines 1-5 and col. 9, lines 62 to col. 10, lines 5, as directed to claims 5-8. Thus, those skill in the art will know the employment of other bulking agent (such as sucrose) for activated protein C for use in the formulations of the invention and their effective concentrations.

Therefore, in view of the above, one of ordinary skill in the art would have been motivated at the time the invention was made to adapt the well known lyophilization process and addition of pharmaceutically acceptable bulking agent scheme of Foster et

al. secondary reference into the method of gryogranulation of Tse et al. primary reference because including such features into the method of Tse et al. reference would have been obvious to one of ordinary skill in the art to obtain the known and recognized functions and advantages of addition of bulking agents thereof. Thus, the combined teachings of the prior art make obvious a process of preparing cryogranules of activated protein C and a lyophilized formulation having a pharmaceutically acceptable bulking agent thereof.

Therefore, it is made obvious by the combined teachings of the prior art since the instantly claimed invention which falls within the scope of the combined teachings of the prior art method would have been *prima facie* obvious from said prior art disclosure to a person of ordinary skill in the art because as held in host of cases including *Ex parte Harris*, 748 O.G. 586; *In re Rosselete*, 146 USPQ 183; *In re Burgess*, 149 USPQ 355 and as exemplified by *In re Best*, "the test of obviousness is not express suggestion of the claimed invention in any and all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them".

ACTION IS FINAL

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

CONCLUSION AND FUTURE CORRESPONDANCE

7. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abdel A. Mohamed whose telephone number is (571) 272-0955. The examiner can normally be reached on Monday through Friday from 7:30 a.m. to 5:00 p.m. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher S.F. Low, can be reached on (571) 272-0951. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306 for regular communications and (703) 305-7401 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Christopher S. F. Low

CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

AAM Mohamed/AAM

February 17, 2004